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Drury, Nigel; Stoll, Victoria; Bond, Chris; Patel, Akshay; Hutchinson, Suzie; Clift, Paul

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Original Article

*Collaborators:

Patients and parents: Emma Adams, Isabel Baumber, Kerry Crofts, Sally Evans, Donna Giles, Wendy Knowles, David Simpson, Anthony Smith, Patrick Smith; Birmingham Children's Hospital: Mr David J Barron, Mr William J Brawn, Dr Rami Dhillon, Dr Haifa Eltayeb, Ms Natasha E Khan, Justine Kidd, Julie C Menzies, Prof Kevin P Morris, Jacqui Nisbett, Nikki Rehman, Dr Anna N Seale, Dr Oliver Stumper; Bristol Royal Children's Hospital: Mr Andrew J Parry; Evelina London Children's Hospital: Dr Hannah R Bellsham-Revell; Great Ormond Street Hospital, London: Mr Ben Davies; Little Hearts Matter: Lexie Katsatis; Newcastle University & Freeman Hospital, Newcastle: Dr Bill Chaudhry, Dr Louise Coats; Queen Elizabeth Hospital Birmingham: Tom Gaffey, Nichola Pope, Mr Ivan Yim; The Somerville Foundation: John Richardson; University Hospital Southampton: Dr Catherine L Mercer; University of the West of England: Dr Lyvonne N Tume; University of Worcester: Dr Kerry L Gaskin.

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Author for correspondence:

Dr N. Drury, Department of Paediatric Cardiac Surgery, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK.
Tel: +44 121 333 8731;
E-mail: n.e.drury@bham.ac.uk

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Research priorities in single-ventricle heart conditions: a United Kingdom national study

Nigel E. Drury^{1,2}, Victoria M. Stoll^{2,3}, Chris J. Bond¹, Akshay J. Patel^{1,2}, Suzie Hutchinson⁴ and Paul F. Clift^{2,3} on behalf of the collaborators*

¹Department of Paediatric Cardiac Surgery, Birmingham Children's Hospital, Birmingham, UK, ²Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK, ³Department of Adult Congenital Cardiology, Queen Elizabeth Hospital Birmingham, Birmingham, UK and ⁴Little Hearts Matter, Birmingham, UK

Abstract

Objective: To bring together stakeholders in the United Kingdom to establish national priorities for research in single-ventricle heart conditions. **Methods:** This study comprised two surveys and a workshop. The initial public online survey asked respondents up to three questions they would like answered for research. Responses were classified as unanswered, already answered, or unable to be answered by scientific research. In the follow-up survey, unanswered questions were divided into categories and respondents were asked to rank categories and questions by priority. A stakeholder workshop attended by patients, parents, healthcare professionals, researchers, and charities was held to determine the final list of research priorities. **Results:** A total of 128 respondents posed 344 research questions, of which 271 were classified as unanswered, and after removing duplicates, 204 questions remained, which were divided into 20 categories. In the second survey, 56 (49.1%) respondents successfully ranked categories and questions. A total of 39 participants attended the workshop, drawing up a list of 30 research priorities across nine priority categories. The nine priority categories are: Associated co-morbidities; Brain & neurodevelopment; Exercise; Fontan failure; Heart function; Living with a single ventricle heart condition; Management of the well-functioning Fontan circulation; Surgery & perioperative care; and Transplantation, mechanical support & novel therapies. **Conclusions:** Through a multi-stage process, we engaged a wide range of interested parties to establish a list of research priorities in single-ventricle heart conditions. This provides a platform for clinicians, researchers, and funders in the United Kingdom and elsewhere to address the most important questions and improve outcomes in these rare but high-impact CHDs.

Single-ventricle heart conditions are a collection of congenital cardiac defects in which one of the ventricles is insufficiently developed or compromised such that it is unable to support an adequate cardiac output. With an incidence of 2–3 in 10,000 live births,^{1,2} it includes diagnoses such as hypoplastic left heart syndrome, tricuspid atresia, and unbalanced atrioventricular septal defect. Although initial surgical palliation varies by type, their paths commonly converge around 3–4 years of age to undergo the Fontan procedure,³ whereby the functioning ventricle is used to support the systemic circulation with passive blood flow in series to the lungs. The success of surgical programmes over the last 30 years has led to an increasing number of children and adults living with a Fontan circulation, currently estimated at over 3000 in the United Kingdom,¹ and up to 70,000 worldwide,⁴ with the population predicted to double over the next 20 years in developed countries.^{1,5} However, this inherently inefficient circulation predisposes to multiple late complications,^{6,7} with half affected by a major complication before reaching adulthood.⁸ A 40-year-old patient with Fontan physiology has an 18% 5-year risk of death, comparable to that of a 75-year-old in the general population of United Kingdom.⁹

Patients with single-ventricle heart conditions have complex healthcare needs, requiring multiple operations often from birth and lifelong, multi-disciplinary follow-up in specialist centres.¹⁰ Ongoing physiological and psychosocial issues place a considerable burden on patients and their families with a significant reduction in quality of life.¹¹ Although there are expectations of improving outcomes,¹² the Fontan circulation remains a life-limiting condition with limited treatment options; it is the highest risk diagnosis for heart transplantation, yet is the least amenable to mechanical circulatory support.¹³ Consequently, there is a demand for research to understand the impact of living with this condition and improve outcomes for patients and families

throughout their journey. The International Fontan Interest Group has been established as a collaborative initiative to improve outcomes and has called for engagement of stakeholders to direct research priorities.⁴ We therefore brought together interested parties in the United Kingdom to establish priorities for research in single-ventricle heart conditions.

Materials and methods

The study was developed in collaboration with *Little Hearts Matter*, the United Kingdom national charity for single-ventricle heart conditions.¹⁴ As it blurred the boundaries between scientific research and public engagement,¹⁵ approval was obtained from the Ethical Review Committee, University of Birmingham (ERN_17-0902). Our methodology was informed by the James Lind Alliance¹⁶ and Cochrane Tobacco Addiction Group,¹⁵ as we explicitly aimed to reach a wide range of stakeholders including patients, their relatives, healthcare professionals, researchers, charities, funders, and policymakers. The study comprised three stages: an initial public survey; a follow-up ranking survey of respondents; and a workshop of invited parties.

Stage 1 survey: identifying gaps in knowledge

An initial cross-sectional, self-administered, public survey was conducted using REDCap, a secure online platform.¹⁷ An electronic link was disseminated by two national patient charities, *Little Hearts Matter* and *The Somerville Foundation*, via e-mail, newsletters, and social media such as Facebook and twitter. Professional groups were contacted via the organisational mailing lists of the British Congenital Cardiac Association (BCCA), Society for Cardiothoracic Surgery (SCTS) and Paediatric Intensive Care Society Study Group (PICS-SG), and publicised at national meetings. United Kingdom-based researchers, heart charities, research funders, and National Health Service commissioners of congenital heart services were contacted directly via e-mail.

Respondents were asked: "What questions would you like to see answered by future research for patients who have a single-ventricle heart condition?" and invited to pose up to three questions. Additional demographic data was collected on their role, age (patients), relationship with a patient (relatives), and institution (professionals). Consent was obtained for the storage, analysis, and anonymous reporting of data, and a study e-mail address was provided to enable withdrawal of consent and/or data, if required. Respondents were asked to provide their name and e-mail address to allow re-contact for stage 2.

The survey remained open for 12 weeks after which all responses were collated and reviewed according to a pre-determined process.¹⁵ Submitted questions were screened by at least two reviewers (N.E.D., V.M.S., C.J.B., A.J.P.) to remove duplicates and any that fell outside the scope of the study. The remaining questions were rephrased for clarity and consistency of terminology, as required, and classified according to the current literature: as *unanswered* by current research; *already answered* by published research; or *unable to be answered* by scientific research. Any disagreements were resolved by consensus, involving an additional reviewer (P.F.C.) when necessary. Questions considered *unable to be answered* by research were discarded whereas those most commonly deemed to be *already answered* were collated and lay summaries of the explanation with supporting evidence published in the *Little Hearts Matter* newsletter. Valid *unanswered* research questions were allocated into one or more topic categories according to emerging themes and progressed to the next stage.

Stage 2 survey: prioritising gaps in knowledge

Respondents who provided an e-mail address were sent a personalised link to a second REDCap survey, enabling tracking of responses and targeted reminders. Participants were asked to rank the emerging research categories of stage 1 in order of priority for future research, from 1 = "most important" to 20 = "least important". For their top three categories, they were asked to similarly rank each question within each category.¹⁵

The second survey remained open for 4 weeks with a reminder sent after 2 weeks. Fisher's exact test was used to compare response rates. Any responses with insufficient data were excluded. Completed responses were collated and categories assigned a score inversely proportional to their ranking, such that the highest-ranked scored 20 points down to 1 point for the lowest-ranked; a category received an additional 10 points each time it was ranked in a respondent's top three. By combining these scores, the highest-ranking categories were taken forward to the next stage, along with the 5–7 highest ranking questions in each.

Stage 3 workshop: establishing research priorities

Participants were invited to take part in the workshop to represent all those affected by, caring for, or conducting research into single-ventricle heart conditions. An iterative process of invitation was used to ensure an adequate balance by role, age/experience, gender, and location, with the first invitations sent out 8 weeks in advance. Patients and parents who had responded to the surveys were contacted via e-mail, with further participants recruited via social media. A broad range of healthcare professionals were invited from every tertiary CHD programme in England.

Workshop participants were provided with a booklet in advance, containing information about the study and the list of categories and questions prioritised at stage 2. Written consent was obtained for participation, digital recording of discussions, data sharing, and being named as a collaborator. The workshop comprised small and large group discussions chaired and facilitated by N.E.D., with participants seated at round tables of six or seven according to a pre-determined plan to achieve mixed groups by role, experience, and location; this ensured that patients/parents were not on the same table as their direct healthcare providers. All participants were encouraged to share their views, respect the views of others, and ensure that they all had the opportunity to express their opinions. Specialist nurses and charity representatives were available throughout the day so that participants could talk through any difficult issues in a private breakout room.

In the morning, the small groups were asked to identify which five categories were highest priority for their table and present their choices and reasons to the whole group. Over lunch, responses were collated using a nominal group technique to generate a final list of nine priority categories and these were fed back to the whole group. The small groups were then allocated three priority categories that they had chosen such that each category was independently reviewed by two tables. They were asked to prioritise three questions within each of these categories, present their choices to the whole group, and following discussion, group consensus was sought on the three most important questions in each category. The workshop closed with an open discussion on how the community should take forward research in single-ventricle heart conditions. Anonymous feedback cards were provided and individual comments collated.

Results

Stage 1 survey

The initial survey was open from 9 October to 31 December, 2017. A total of 128 individuals completed the online form, of whom 49 (38.3%) were adult patients or family members (Table 1); patients ranged from 16–24 years to 65+ years. Although it is assumed that most respondents were from the United Kingdom, responses are known to have been submitted from professionals in continental Europe, North America, and Africa.

Respondents posed 340 research questions: 94 with three questions, 24 with two questions, and 10 with one question; on review, four composite questions were split to improve clarity, giving a total of 344 questions. Of these, 271 (78.8%) were classified as *unanswered*, 26 (7.6%) as *already answered*, and 47 (13.7%) as *unable to be answered*. After removing duplicates and rephrasing for clarity and consistency as required, 204 unanswered questions remained which were divided into 20 categories according to emerging themes.

Stage 2 survey

A total of 114 (89.1%) respondents to stage 1 provided an e-mail address and were re-contacted in February 2018. Of 114 respondents, 65 (57.0%) completed the follow-up ranking survey, of whom 25 (38.5%) were adult patients or family members (Table 1); there was no significant difference between the response rates of patients/family members and healthcare professionals ($p=0.85$). Nine (13.8%) responses were discarded due to insufficient data or inappropriate completion and 56 (86.2%) were analysed. The scoring of categories and frequency of ranking

in the top three are shown in Table 2. A full list of the categories and questions taken forward to the workshop is documented in the supplementary material.

Stage 3 workshop

The final-stage workshop was held in a meeting venue in central Birmingham, United Kingdom on Monday 23 April, 2018 and was attended by 39 participants representing a wide range of perspectives (Table 1). An additional 10 adult patients, 5 parents, 12 healthcare professionals, and 2 researchers were invited during the iterative process but declined; healthcare professionals from all 10 tertiary CHD programmes in England were invited of which six were represented; see the list of collaborators. They were categorised into nine categories were prioritised by at least two tables and taken forward. On discussing the questions in each category, there was a lack of consensus in two categories, and it was agreed that more than three questions would be retained as priorities in each. The workshop felt that some questions should be reworded to combine the aspects of separate questions. Furthermore, the group felt it was important to broaden the category of *transplantation, mechanical support, and stem cell therapy* by renaming it as *transplantation, mechanical support, and novel therapies* as there was apprehension over the unproven role of stem cells, despite much interest from survey respondents. The final list of 30 research priorities determined by the workshop is shown in Table 3.

In the closing discussions, several key themes emerged:

- Collaboration among the United Kingdom CHD community, to bring together all centres in a network and establish a working group of key stakeholders;

Table 1. Roles of participants in the surveys and workshop.

| Role | Initial survey stage 1 (n = 128) | Ranking survey stage 2 (n = 65) | Workshop stage 3 (n = 39) |
|------------------------------------|----------------------------------|---------------------------------|---------------------------|
| Adult patients | 7 | 2 | 4 |
| Patient family members | 42 | 23 | 5 |
| Parents | 38 | 20 | 5 |
| Partners | 3 | 3 | 0 |
| Child | 1 | 0 | 0 |
| Healthcare professionals | 71 | 34 | 23 |
| Paediatric cardiologists | 13 | 6 | 5 |
| Adult congenital cardiologists | 9 | 7 | 4 |
| Cardiac surgeons | 13 | 7 | 7 |
| Cardiac anaesthetists/intensivists | 9 | 4 | 1 |
| Paediatric nurses | 15 | 5 | 3 |
| Adult congenital nurses | 3 | 2 | 2 |
| Other* | 8 | 3 | 1 |
| Researchers | 7 | 5 | 4 |
| Charity representatives | 1 | 1 | 3 |
| Policy makers | 0 | 0 | 0 |

*Stage 1: 2 cardiac physiologists, 2 cardiac radiologists, 1 clinical perfusionist, 1 data analyst, 1 paediatrician with expertise in cardiology, 1 surgical care practitioner. Stage 2: 1 cardiac radiologist, 1 data analyst, 1 paediatrician with expertise in cardiology. Stage 3: 1 clinical geneticist.

Table 2. Scoring of categories in the ranking survey (stage 2).

| Category | Ranking points | Rank #1 | Rank #2 | Rank #3 | Rank #1-3 | Total score | Proceed to workshop |
|---|----------------|---------|---------|---------|-----------|-------------|---------------------|
| Fontan failure | 818 | 11 | 10 | 5 | 26 | 1078 | Yes |
| Transplantation, mechanical support and stem cell therapy | 658 | 10 | 2 | 5 | 17 | 828 | Yes |
| Heart function | 713 | 6 | 4 | 0 | 10 | 813 | Yes |
| Outcomes of current treatments | 691 | 6 | 1 | 5 | 12 | 811 | Yes |
| Management of the well-functioning Fontan circulation | 666 | 4 | 6 | 3 | 13 | 796 | Yes |
| Anticoagulation | 646 | 2 | 4 | 5 | 11 | 756 | Yes |
| Alternatives to a Fontan circulation | 585 | 3 | 6 | 5 | 14 | 725 | Yes |
| Associated co-morbidities | 649 | 0 | 4 | 3 | 7 | 719 | Yes |
| Living with a single-ventricle heart condition | 638 | 0 | 2 | 4 | 6 | 698 | Yes |
| Quality of life | 617 | 4 | 3 | 1 | 8 | 697 | Yes |
| Arrhythmias | 623 | 3 | 1 | 3 | 7 | 693 | Yes |
| Exercise | 618 | 0 | 2 | 3 | 5 | 668 | Yes |
| Brain and neurodevelopment | 594 | 1 | 1 | 5 | 7 | 664 | Yes |
| Surgery and perioperative care | 527 | 2 | 2 | 4 | 8 | 607 | Yes |
| Low oxygen saturations/cyanosis | 566 | 1 | 0 | 0 | 1 | 576 | – |
| Counselling and parental support | 518 | 0 | 3 | 1 | 4 | 558 | – |
| Liver function | 520 | 0 | 3 | 0 | 3 | 550 | – |
| Psychological impact | 498 | 2 | 1 | 1 | 4 | 538 | – |
| Causes of single-ventricle heart conditions | 488 | 0 | 2 | 3 | 5 | 538 | – |
| Pulmonary vascular development and function | 451 | 1 | 0 | 1 | 2 | 471 | – |

- Establishment of a national registry for the long-term follow-up of patients with single-ventricle heart conditions, learning from the experiences of the Australia and New Zealand Fontan Registry;¹²
- Standardisation of follow-up protocols and recording of a core set of variables to facilitate the registry;
- The importance of continuing to involve patients, their families, and charities in these processes;¹⁸
- The need for diverse research methodologies to answer the prioritised questions;
- Engagement with multi-disciplinary researchers, such as engineers, biologists, geneticists, social scientists and industry, and with colleagues across the world through the International Fontan Interest Group.⁴

Finally, all patients and parents agreed that their voices had been heard during the workshop and this was supported by individual comments on anonymous feedback cards.

Discussion

Prioritisation of research through consultation with those affected by or caring for those with a disease ensures that it remains directly relevant to improving their lives. In this study, we sought to establish priorities for research in single-ventricle heart conditions by engaging with a wide range of stakeholders, including

adult patients, parents, healthcare professionals, researchers, and charities. Through a multi-stage process, we compiled a list of potential questions, filtered out those already answered or unanswerable, removed duplicates, rephrased for clarity and consistency, re-consulted to prioritise questions, convened a diverse group of interested parties, and produced a validated final list of priorities. To our knowledge, this study is the first to bring together stakeholder groups to establish specific priorities for research in single-ventricle heart conditions and thereby shape the research agenda.

Several studies have assessed research priorities in CHD including single-ventricle heart conditions. Cotts et al for the Alliance for Adult Research in Congenital Cardiology compiled a list of 45 questions and conducted a survey of providers to identify 10 priority questions, with some input from patient groups.¹⁹ Of these, four were specific to patients with single-ventricle heart conditions: “Is pulmonary vasodilator therapy beneficial in Fontan patients?”, “Are warfarin and/or aspirin beneficial in preventing primary thromboembolic events in adult Fontan patients?”, “What is the optimal medical therapy for preservation of ventricular systolic and diastolic function in Fontan patients?” and “What is the optimal medical treatment algorithm for Fontan patients with protein-losing enteropathy?”, whereas another was also relevant: “What are the ideal criteria for transplantation referral in ACHD?”. Similar questions to each of these were posed in our initial survey but only preservation of ventricular function was included as a priority. Helm et al

Table 3. Final list of research priorities determined by the workshop (stage 3).

| Category | Research question |
|--|--|
| Associated co-morbidities | What are the outcomes in children with multiple co-morbidities? |
| | What are the common co-morbidities in children with a single-ventricle heart condition? |
| | What is the impact of syndromes or other co-morbidities on the quality of life of those with a single-ventricle heart condition and their families? |
| Brain and neurodevelopment | What factors influence neurodevelopmental outcomes in children with single-ventricle heart conditions? |
| | Are there differences in brain development in the fetus with a single-ventricle heart condition and if so, what is the impact on outcomes? |
| | What is the impact of a single-ventricle heart condition on neurodevelopment? |
| Exercise | What are the effects of regular physical exercise on well-being and long-term outcome in the Fontan circulation? |
| | What type of exercise is most beneficial in those with a Fontan circulation? |
| | What are the benefits of exercise rehabilitation in well and deteriorating patients with a Fontan circulation? |
| Fontan failure | What are the best markers of deterioration in patients with a Fontan circulation? |
| | What is the main mechanism behind failure of the Fontan circulation? |
| | How can we prevent late multi-organ dysfunction in the Fontan circulation? |
| Heart function | What is the cause of ventricular dysfunction in the single ventricle? |
| | How can ventricular function be best preserved in patients with a single-ventricle heart condition? |
| | What treatments can be developed for ventricular failure in patients with a Fontan circulation? |
| Living with a single-ventricle heart condition | What are the frequencies of symptoms, limitations, physical, and emotional quality of life with a Fontan circulation? |
| | What lifestyle choices (e.g. diet, exercise, occupation, physical location) best support the long-term health of patients with a single-ventricle heart condition? |
| | What are the long-term social, psychosocial, and other non-clinical outcomes of children with single-ventricle heart conditions? |

Table 3. (Continued)

| | |
|--|---|
| | Which models of care, virtual ward and home monitoring programmes, best support infants, children and young people with a single-ventricle heart condition at home? |
| Management of the well-functioning Fontan circulation | How can the longevity of the Fontan circulation be prolonged? |
| | How can organ function be optimised in patients with a Fontan circulation? |
| | What factors best determine a well-functioning Fontan circulation? |
| | What is the optimal interval for follow-up of patients with a Fontan circulation? |
| | What is the impact of pregnancy on patients with a Fontan circulation and how can outcomes be improved? |
| Surgery and perioperative care | Which modifiable perioperative factors can reduce mortality for the Norwood operation? |
| | How can perinatal risk stratification be used to identify those in whom the Norwood operation is futile? |
| | How could technology be used to perform a biventricular repair in patients with a single-ventricle heart condition? |
| Transplantation, mechanical support, and novel therapies | How can mechanical assist devices be developed to support the Fontan circulation? |
| | What are the roles of novel therapies in the failing Fontan? |
| | What are the alternatives to transplantation for the failing Fontan? |

conducted an online survey of adult patients, relatives, and physicians to prioritise pre-determined research topics, including in the Fontan circulation;²⁰ priorities included the failing Fontan, catheter ablation and rhythm disorders, sex and pregnancy, diagnostic imaging, and quality of life. Finally, McCrindle et al convened a working group to explore issues specific to thrombosis in children, including those with single-ventricle heart conditions;²¹ despite not including patients or the public in the group, they concluded that patients and their families are important stakeholders in designing successful studies and identified patients with a single ventricle as a priority population for research.

The priorities identified in our study comprise 30 research questions across nine categories. Several categories which scored highly in the ranking survey (Table 2), notably *outcomes of current treatments*, *anticoagulation*, and *alternatives to Fontan*, were deemed less important by the workshop participants than some lower ranking categories: *exercise*, *brain and neurodevelopment*, and *surgery and perioperative care*. This may reflect specific interests of those attending the workshop or that recognition of the importance of these categories was elevated through the

workshop discussions. In addition, *quality of life* was felt to significantly overlap with aspects of other categories which ranked higher. The final list of priorities addresses a wide range of issues impacting on those affected by single-ventricle heart conditions – from perinatal decision-making to late multi-organ dysfunction, surgical technology to lifestyle choices, and mechanisms of disease to quality of life. Consequently, diverse methodologies will be required to address these questions, including surveys, qualitative studies, translational research, and clinical trials, driving collaboration within the CHD community and across disciplines. Our findings will be publicised nationally, including in charity newsletters and via social media, and we will engage with the National Institute for Health Research, other research funders, and National Health Service specialised commissioning to promote awareness of the priorities identified.²²

In this study, we deliberately adopted an approach different to that advocated by the James Lind Alliance to enable us to engage with stakeholders beyond patients, carers, and clinicians.¹⁶ We also wanted to generate more than 10 priority questions as single-ventricle heart conditions are lifelong, multi-system disorders that impact on patients and their families throughout their lives. Other strengths included triangulation of the survey and workshop to provide different perspectives, reduce bias, and enhance the validity of the findings;²³ engagement with a wide range of healthcare professionals involved in the care of these patients; mixed yet balanced groups on each table to facilitate open discussion, whilst avoiding seating patients or parents with their direct healthcare providers; and obtaining funding to cover travel expenses for patients and parents to attend the workshop. In addition, it provided an opportunity to resolve questions already answered by published research, educate and dispel myths in the wider community.

Limitations

There were several limitations to this study. First, the mechanisms used to publicise the survey attracted a predominately United Kingdom-based audience potentially limiting the international applicability of the questions generated, although there were known to be responses from elsewhere; in addition, the workshop attendees were exclusively living or working in the United Kingdom which may have impacted on which categories and research questions were prioritised. The number of adult patients who replied to the initial survey was lower than expected but the response from parents was encouraging. This may have shifted the focus towards paediatric matters, such as diagnosis and surgery, with less attention on later issues, such as longevity and end of life care, although the two highest ranking categories were Fontan failure and transplantation. We invited a range of clinical and research policymakers to participate in the study but none responded, thereby reducing the scope of potential questions regarding resource utilisation and comparative effectiveness. The second stage of the survey was more complex than the first which may have reduced the response rate and the software was not able to adequately enforce the rules for completion, leading to the exclusion of nine incomplete or inappropriate responses. The workshop was held on a weekday to facilitate attendance by healthcare professionals but was seen to impact on the ability of working patients and parents to attend, either directly or through the need for childcare; this may also have skewed the demographic of those present. Furthermore, there was no specific travel funding for professional attendees which may have impacted on

how far they were prepared to travel. Finally, our two centres in Birmingham were disproportionately represented at the workshop; although we have the largest surgical and adult programmes for the management of these conditions in the United Kingdom,²⁴ the debate could have been unduly influenced by local practices and the final list of priorities has not been externally validated.

Conclusions

We used a multi-stage process to bring together all interested parties to establish a list of priorities for research in single-ventricle heart conditions. Our findings provide a platform for clinicians, researchers, and funders in the United Kingdom and elsewhere to address the most important questions and drive forward research to improve outcomes in these rare but high-impact CHDs.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/S104795111800224X>

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The study data were collected and managed using REDCap electronic data capture tools hosted at the University of Birmingham. REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources.¹⁷

Contributors. N.E.D., S.H., and P.F.C. devised the study. N.E.D., V.M.S., and P.F.C. obtained funding. N.E.D. coded the electronic surveys. N.E.D., V.M.S., C.J.B., and A.J.P. reviewed the questions and revised the wording, with P.F.C. as the additional reviewer, as required. N.E.D. chaired the workshop which was attended by all authors and collaborators. N.E.D. wrote the first draft of the manuscript which was critically revised by all authors.

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Conflicts of Interest. Dr Clift has received consultancy fees and honoraria from Actelion Pharmaceuticals Ltd. No other authors declare a potential conflict of interest.

Ethical Standards. The authors assert that this work complies with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Ethical Review Committee at the University of Birmingham, United Kingdom.

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